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LETTER TO THE EDITOR

Correlation of c-fos, p53, and PCNA Expression with Treatment Outcome in Osteosarcoma

Dear Sir,

Histologic response to chemotherapy is considered the most important predictor of long-term outcome in osteosarcoma [1–3]. Low levels of necrosis portend an ominous outcome with higher chances of local recurrence and metastasis. If this subset of patients can be identified before therapy is begun, drug selection and dosage schedules can be modified to achieve optimum results [2]. The expression of c-fos, p53, and PCNA has been studied in osteosarcomas, but this is the first study to investigate their value in predicting the treatment outcome.

Formalin-fixed paraffin-embedded tissue from pretreatment biopsies from 13 cases of osteosarcoma (mean age: 21.6 years; 7 males, 6 females) was immunostained with antibodies against c-fos, p53, and PCNA. The patients had received 10 weeks of chemotherapy (doxorubicin, cisplatin, and high-dose methotrexate) followed by surgery. Tumor necrosis was evaluated in post-therapy specimens, and the effect of chemotherapy was divided into 2 groups: good response (> 90% necrosis) and poor response (< 90% necrosis). All the slides were evaluated independently by 2 observers. For c-fos and p53, the intensity of staining was scored as negative or positive. For PCNA, the percentage of positive tumor cells was determined by counting 500 cells (PCNA index). The results were divided into 2 groups: low PCNA index (< 40%) and high PCNA index (> 40%). The association between expression of c-fos, p53, and PCNA and tumor necrosis following chemotherapy was determined using the Fisher exact test.

Of the 13 cases, 8 showed poor response to chemotherapy and all of them were positive for c-fos (Table 1). Five cases responded well to therapy and only 1 was positive for c-fos ($P = 0.007$). Staining was seen in the fibroblastic and chondroblastic areas but was most intense in the osteoblastic areas (Fig. 1). No correlation of tumor necrosis was observed with p53 or PCNA.

Immunohistochemical demonstration of c-fos in pretreatment biopsy in osteosarcoma may be helpful in identifying patients destined to respond poorly to chemotherapy. c-fos is a proto-oncogene that is associated with many biological processes including transcription, regulation of gene expression, cell growth, and cell differentiation, especially in differentiation of osteoblasts and chondrocytes [4]. Overexpression of c-fos was observed in 61% of human OS [5]; high levels have also been reported in murine OS and OS cell lines [6]. Correlation of p53 and PCNA with tumor necrosis was not statisti-

TABLE I. Histologic Response to Chemotherapy for Osteosarcoma

Tumor necrosis after chemotherapy	c-fos		p 53		PCNA index	
	POS	NEG	POS	NEG	<40%	>40%
90%–100% (n = 5)	1	4	4	1	1	4
0%–90% (n = 8)	8	0	4	4	5	3
	$P = 0.007$		$P = 0.31$		$P = 0.20$	

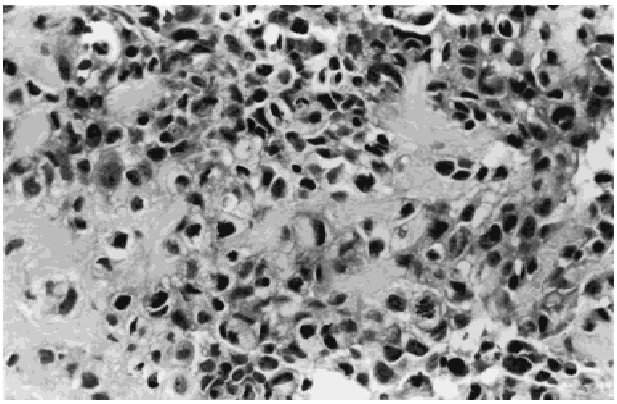

Fig. 1. c-fos immunoperoxidase staining in osteosarcoma. (400×, original).

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cally significant. Although derived from a small number of patients, our results are encouraging and suggest that strong c-fos expression is highly correlated with poor response to chemotherapy.

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